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# The Evolving Landscape of Drug Resistance: From Mechanisms to Therapeutic Strategies

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***Abstract:***

Drug resistance is a major factor that frustrates the treatment of the disease in patients. This issue is multifactorial in nature because it involves a complex interaction between genetic and epigenetic modifications, drug-metabolizing, enhanced DNA repair, efflux pump systems, and interactions in the tumor microenvironment. Recent developments in molecular biology, such as next-generation sequencing and CRISPR-Cas9, have shed some light on these complex resistance mechanisms, leading to the discovery of new therapeutic targets. New approaches, which include combination therapy, immunotherapy, and nanomedicine, provide an effective way to fight resistance. Nevertheless, biomarkers, personalized medicine and tumor microenvironment have to be further explored, as they will help to make cancer care more effective in overcoming this chronic problem. This review aims to summarize the latest knowledge on drug resistance mechanisms in cancer, the emergence of therapeutic options to overcome this resistance and share future research advances in this most fundamental field.

**Keywords:** Drug resistance, Cancer therapy, Immunotherapy, Nanomedicine, Personalized medicine.

## Introduction

Cancer is a multifaceted disorder characterized by the uncontrolled growth and spread of abnormal cells. It is the consequence of damage inflicted on DNA, the molecule responsible for controlling cellular functions and growth (1). Changes in DNA can occur in oncogenes, which mandate the growth of cells, and in tumor suppressor genes, which can modify cell growth in a protective manner. Changes in these genes allow cells to grow without control, forming tumors that can invade adjacent tissues and metastasize to distant sites (2). It may Cancer development may result from multiple factors, including genetic, environmental, and lifestyle determinants. Certain genetic mutations can be inherited, increasing the relative risk for developing some types of tumors.



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Considered environmental risk factors are tobacco smoke, asbestos, and ultraviolet light, which can damage DNA and increase the risk of cancer. Also, diet, physical activity, and consumption of alcohol are accepted to be important risk factors (3). Cancer therapy has changed significantly over the last decades and now offers different approaches depending on the type and stage of cancer. It may include surgery to remove the tumorous tissue, radiation therapy to destroy the malignant cells with high-energy beams, chemotherapy to administer drugs that act on rapidly dividing cells, and cancer-specific therapies aimed at cancer cell vulnerabilities (4). Another increasingly important therapeutic option is immunotherapy, which employs the immune system to fight cancer. Cancer therapy is also associated with certain challenges, notwithstanding these developments. Most therapeutic modalities, while effective in targeting malignant cells, may also adversely affect healthy cells. Another significant challenge is drug resistance, whereby cancer cells may find a way to bypass the effects of treatments (5).

Drug resistance is a serious impediment to the effective therapy of cancer, oftentimes resulting in disease recurrence and worse outcomes for the patient. Due to the underlying genetic instability and rapid proliferation, cancer cells can counteract the destructive effects of anticancer therapies (6). This resistance can take the form of reduced cellular uptake of the drug, increased drug efflux, alteration of the drug's modification resistance to the targeted pathways said drug interacts with, stimulation of bypass pathways that supersede the drug's intended function, enhanced repair mechanisms that counteract the damage of certain DNA and chemoperes (7). The mechanism underlying the development of drug resistance is complex and involves a selection pressure. In the presence of a treatment, malignant cells that can mount a resistance response are the ones that survive, multiply, and in the end, dominate the tumor, and therefore, the malignant cells within the tumor grow and thrive (8).

The emergence of drug resistance can result from many interrelated processes. Either spontaneous or treatment-based genetic alterations affect the relevant proteins of action or drug metabolism. On the other hand, the contributing factor of interest (9) can be some of the molecular changes, like alteration of the methylation marks or modification of the histones, which regulate processes of critical importance, such as drug metabolism or the longevity of the cell. In addition, elements of the tumor microenvironment can contribute to drug resistance. Hypoxia, alongside some immune cell types (10), can pose selective resistance to troublesome drug-resistant cells. All of these considerations are essential for the prevention and minimization of multidrug resistance and increasing the efficacy of cancer treatments. The primary focus of this study is the processes that create barriers to effective treatment for cancer, and the obstacles that medication resistance creates. The study specifically aims to enhance treatment outcomes by overcoming challenges posed by medication resistance.

## Mechanisms involved in drug resistance

### *Efflux pumps*

Efflux pumps especially those in the ATP-binding cassette (ABC) transporter family are central to cancer cells' ability to resist multiple drugs, actively transporting drugs out of the cell repeatedly, reducing intracellular drug accumulation, and repeatedly expelling drugs from the cell. These pumps are located in the cell membrane and actively transport a wide range of substances, including anticancer drugs, out of the cell, thereby reducing intracellular drug accumulation. Efflux pumps actively reduce intracellular drug concentrations, preventing therapeutic agents from reaching their molecular targets (10). At this lower dose, tumor cells keep multiplying despite the chemotherapy in their system. Persistent efflux pump activity enables tumor cells to survive and proliferate despite chemotherapeutic pressure, and the treatment ultimately fails. Researchers have taken a close look at numerous ABC transporters like P-glycoprotein (P-gp/ABCB1), multidrug resistance–associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2) and linked them to multidrug resistance across many types of cancer. Other resistance tricks such as tweaking drug targets or ramping up DNA repair can join forces

with efflux pumps, rendering cancer cells resistant to treatment, thereby rendering cancer cells resistant to conventional therapies. To beat multidrug resistance and make cancer treatments work better, researchers need to pinpoint the exact efflux pumps fueling a specific tumor and grasp what drives them like low oxygen in the tissue or the strain of repeated drug doses (13).

***Epigenetic modifications***

Heritable epigenetic alterations which do not alter DNA sequences play an essential part in creating and supporting cancer cell resistance to treatments. The three types of epigenetic modifications, including DNA methylation and histone modifications, and microRNA changes, can alter gene expression patterns, which affect drug metabolism genes and therapeutic targets and cell survival genes and DNA repair mechanisms, thus reducing medication efficacy (14). The silencing of tumor suppressor genes through promoter hypermethylation enables cells to proliferate and potentially leads to resistance against treatments that focus on rapidly dividing cells. The under-methylation of oncogenes leads to their excessive expression, which drives both increased cell growth and treatment resistance. Reversible epigenetic alterations in cancer cells offer potential therapeutic avenues to enhance drug efficacy could be reversed, creating new treatment possibilities to enhance medication effectiveness (15).

P-glycoprotein (P-gp) serves as a well-studied example of drug resistance, which receives epigenetic regulation through its gene expression. The high expression levels of P-gp enable tumor cells to actively remove chemotherapy drugs, which results in reduced drug effectiveness inside the cells (16). The P-gp promoter undergoes DNA hypomethylation, which increases P-gp expression, resulting in drug resistance development. Histone modifications, including increased histone acetylation, contribute to P-gp gene transcription activation. To develop new treatment approaches for drug resistance, it is necessary to understand how specific epigenetic changes regulate P-gp expression (17). The therapeutic approach employs DNA methyltransferase inhibitors together with histone deacetylase inhibitors to modify cancer cell epigenomes, which enhances their chemotherapy susceptibility.

***Tumor microenvironment***

The tumor microenvironment (TME) functions as a complex dynamic system surrounding cancer cells, which plays a vital part in cancer development, along with metastasis and treatment resistance. The tumor microenvironment contains multiple components, which include fibroblasts together with immune cells, blood vessel endothelial cells and extracellular matrix components (18). The complex network of TME connections provides cancer cells with growth factors and survival signals, plus treatment protection (19). The TME applies selection forces to drug-resistant tumor cells, which leads to treatment failure. The TME environment creates conditions such as oxygen depletion and nutrient scarcity, and acidity, which either select or produce tumor cells that develop enhanced drug resistance mechanisms. The physical characteristics of the TME, such as dense ECM tissue and abnormal blood vessel formation, reduce drug delivery to tumors, which decreases treatment effectiveness (20).

Different cell types in the TME are associated with drug resistance. The TME contains cancer-associated fibroblasts (CAFs), which release growth hormones and ECM components to support tumor cells against drug resistance. These cells modify the extracellular matrix to construct physical barriers which stop drugs from entering the tumor area. Immune cells, which are designed to kill cancerous cells, may create treatment resistance despite their natural function. Tumor-associated macrophages (TAMs) adopt pro-tumor characteristics by producing substances which stimulate tumor cell growth and blood vessel formation, and resistance to treatment (21). Myeloid-derived suppressor cells (MDSCs) represent immune cells that hinder anti-tumor responses while generating treatment resistance through multiple mechanisms. Endothelial cells, which form blood vessel linings, contribute to medication resistance by blocking drug delivery to tumors while sustaining the survival of tumor cells that have spread to distant regions (22). The connection between cancer cells

and various cell types present in the TME creates a complex two-way interaction. Cancer cells influence stromal cell activities, which then provide defense mechanisms to cancer cells, thus creating treatment resistance (23). The multidimensional interactions of the TME necessitate in-depth knowledge in order to create innovative therapeutic options that target cancer cells alongside their supportive cells and their microenvironment. Attacking the protective elements of the TME, such as CAFs and TAMs and ECM structures, can enhance drug delivery while reinstating tumor cell drug sensitivity, thus enhancing cancer treatment outcomes (24).

**DNA repair pathways**

The biological mechanisms that maintain genomic stability work by detecting and repairing different types of DNA damage, including single-strand breaks, double-strand breaks, base modifications and DNA cross-links (25). Several protein complexes combine to identify mutilated DNA, as well as switching up repair machineries that help to repair the DNA sequence. Various DNA repair mechanisms can be found in the cell, with each repairing a particular type of damage. The cellular repair system uses nucleotide excision repair (NER) to remove big DNA lesions from UV radiation and chemical carcinogen exposure, while base excision repair (BER) removes damaged and modified bases (26). Double-strand breaks require both homologous recombination (HR) and non-homologous end joining (NHEJ) processes for repair because this type of damage threatens chromosomal stability and causes cell death. DNA repair mechanisms must function correctly and precisely to maintain normal cell operations and survival, yet defects in these pathways increase mutation rates, which leads to cancer development (27).

Cancer cells that exhibit genomic instability develop better DNA repair mechanisms to defend themselves against DNA-damaging treatments like chemotherapy and radiation. The medicines deliver DNA damage to cancer cells, which triggers apoptosis as a result (28). Tumor cells that possess enhanced DNA repair mechanisms are capable of fixing the damage effectively, which allows them to survive and multiply despite therapeutic interventions. The improved DNA repair capability emerges through different mechanisms, including enhanced DNA repair protein synthesis and elevated repair pathway activity, as well as modifications in DNA repair pathway regulatory networks (29). ERCC1 protein expression levels have been shown to influence resistance against platinum-based chemotherapies, which create cross-linked DNA. The HR pathway expression levels determine radiation resistance against ionizing radiation, which produces double-strand breaks (30).

The relationship between DNA repair systems and drug resistance exists as a complex multidimensional network. The enhancement of DNA repair capability protects tumor cells against DNA-damaging therapies yet increases their vulnerability to alternative therapeutic approaches (31). Tumor cells with defective DNA repair pathways, such as BRCA1/2 in the HR pathway, display increased vulnerability to PARP inhibitors, which disrupt single-strand break repair mechanisms. Synthetic lethality exploits a faulty DNA repair mechanism to increase cancer cell vulnerability to blockages in another cellular process (32). The tumor microenvironment can influence the capability of cells to repair DNA damage. Hypoxia causes damage to the DNA, even as it alters the levels of the proteins in DNA repair that the cells synthesize. The challenge of coming up with a tailored cancer therapy that targets any tumor weakness includes knowledge of the interdependencies between the aspects of DNA repair mechanisms, drug resistance, in addition to tumor environmental conditions (33). The combination of DNA repair mechanisms with drug resistance and tumor microenvironment impacts requires a thorough understanding to develop personalized cancer therapies which focus on specific tumor vulnerabilities (33).

**Drug Resistance: A Challenge in Cancer Therapy**

The effectiveness of cancer therapy depends heavily on drug resistance across different cancers because this resistance decreases treatment success and determines final patient prognosis. A curable malignancy transforms into a potentially fatal illness because of resistance, which limits therapy

options before leading to disease progression and recurrence (34). Different cancer types display this issue to varying degrees because their resistance mechanisms and treatment protocols differ. The major challenge of drug resistance emerges strongly in blood cancers including acute myeloid leukemia (AML) (35). The chemotherapy resistance of AML cells develops through multiple mechanisms, which include increased ABC transporter drug efflux and FLT3 receptor tyrosine kinase target mutations and apoptotic pathway modifications. The mechanisms of resistance often lead to relapse, so patients need to undergo more aggressive and potentially less successful salvage treatment (36). The BCR-ABL1 fusion gene mutations that drive chronic myeloid leukemia (CML) produce resistance to tyrosine kinase inhibitors (TKIs), including imatinib. The mutations prevent the TKI from proper binding, which allows leukemic cells to multiply without control (37).

Solid cancers face significant challenges when their treatments become resistant to the administered therapies. Lung cancer patients develop resistance to EGFR inhibitors, including gefitinib and erlotinib, because of mutations in the EGFR gene, specifically T790M. A mutation in the EGFR protein structure makes this protein unresponsive to the inhibitor (38). HER2-targeted treatment resistance in breast cancer patients emerges from multiple mechanisms, including increased alternative growth factor receptor expression along with HER2 bypassing downstream signaling pathway activation and PTEN tumor suppressor gene loss (39). The BRAF V600E mutation in melanoma develops resistance to BRAF inhibitors vemurafenib and dabrafenib through MAPK pathway reactivation, which happens either by acquiring mutations in pathway components or through bypass signaling activation. Colorectal cancer serves as an example where drug resistance plays a vital role in patient management (40).

The mechanisms of resistance to therapeutic regimens such as FOLFOX or FOLFIRI may occur through multiple pathways, such as a higher expression of DNA repair enzymes, drug metabolism through drug efflux transporters, or alteration of the microenvironment. Acquisition of resistance to targeted therapies, including EGFR blockade (cetuximab, panitumumab) or VEGF blockade (bevacizumab), can also occur through the development of compensatory downstream signaling alterations (KRAS or NRAS), or activation of other angiogenesis factors (41). Platinum resistance in ovarian cancer is a major problem clinically. All mechanisms are related to an increase in DNA repair, changes in drug delivery and increased levels of glutathione. This resistance, in most cases, causes relapse and poor prognosis (42). The reality of medication resistance has major effects on the outcomes of patients. It usually involves more severe and ineffective medicines, thus a worse quality of life, and more side effects of the medicine. In addition, the resistance that at times may come with medications may hamper the treatment, thus bringing about difficulty in the treatment of sickness and, in turn, falling survival rates (43). Fighting medication resistance requires the further analysis of the consequent mechanisms, the development of new treatment approaches, and the implementation of individualized medicine approaches to treatment, which make it individual to the very nature of tumor in a particular patient (44).

**Molecular insights into drug resistance: advancing cancer therapy**

However, recent developments in molecular biology have changed our understanding of cancer drug resistance mechanisms and demonstrate significant potential for the development of more effective therapies. Cutting-edge technologies such as the next-generation sequencing (45) can bring out detailed genomic profiling of the tumor, a complex picture of genetic aberrations, epigenetic changes, as well as the variations in the expression of genes which trigger the emergence of drug resistance (46). Single-cell sequencing tools are being used to help fill in this gap by demonstrating the heterogeneity of resistance to a treatment within a tumor, the identification of discrete groups of resistant cells and their characteristics, as well as unique genetics. These findings can enable scientists to unravel the intricate webs of signaling and molecular interactions that drive drug resistance in order to make new targets of drug therapy and biomarkers (47).

Besides, the CRISPR-Cas9 gene editing technology has gained popularity as a very effective method of drug resistance pathway investigation. Scientists can also add specific mutations to cancer cells with CRISPR or knock out their genes of interest in order to directly see how such modifications impact resistance to treatment (48). Combined with other developed molecular tools, such as proteomics and metabolomics, the potential of the CRISPR tool might create a systems-level understanding of drug resistance that provides insight into how tumor cells change and adapt to selective pressure. The approach has been used to represent drug resistance in vitro, identify novel resistance genes and verify the possibility of a therapeutic target (49).

**Emerging therapies to combat drug resistance**

The challenges posed by cancer-related drug resistance have driven the development of novel therapeutic strategies. Promising drugs are emerging, including the development of next-generation inhibitors against resistant mutations, including the use of third-generation EGFR inhibitors (e.g., osimertinib) against lung cancer patients with T790M resistance mutation (50). Combinations are also becoming more prevalent, trying to hit multiple resistance mechanisms or prevent the selection of resistance. As an example, in melanoma, the use of a BRAF inhibitor plus a MEK inhibitor may act against two critical elements of the MAPK pathway, reducing the probability of the emergence of resistance (51). Another option to overcome the resistance is immunotherapy with the use of the immune system of the body to attack cancer, especially where the mutational load in such tumors is high. Tumor microenvironment manipulation approaches are also under development, such as targeting cancer-associated fibroblasts to disrupt the protective niche that leads to resistance to treatment (52). Finally, the techniques of personalized medicine, based on genetic profiling of individual cancer, are becoming increasingly important to find the most effective medicines and foresee future modes of resistance. Certain instances of this are discussed later (53).

***Effective therapeutic combinations for overcoming drug resistance in cancer***

The phenomenon of drug resistance is a major problem in cancer therapy and often leads to the failure of the therapy and the development of the disease. One of the promising ways to overcome this barrier is to employ combination treatment, i.e. to combine two or more drugs that target multiple pathways and/or mechanisms within tumor cells (54). Combination treatment aims at attacking cancer cells from many angles simultaneously, which makes it more difficult. In theory, additive combinations of medications should have synergistic effects, and therefore, the combination would have greater effects than offered by a combination of the effects produced by the medications (55). Such synergy can be possible through a number of factors, such as one medicine making cancer cells sensitive to the other, or drugs targeting parallel pathways needed by the cancer cells to survive. Combination therapy may also help support resistance processes already present, or the emergence of new resistance mutations (56).

In addition to directing the cancerous cells, combination therapies are also being explored in order to alter the tumor microenvironment and enhance drug transportation. The tumor microenvironment conditions stimulate the proliferation, survival, and metastasis of cancer cells as well as medication resistance (60). It incorporates a wide range of cell types of cells, which include cancer-related fibroblasts, immunological cells, and endothelial cells and beyond the extracellular matrix element. These factors may constitute an inhibitory microenvironment surrounding tumor cells, protecting them against drugs and enhancing drug resistance (61). Coupling chemotherapy with drugs that act on the tumor microenvironment, such as angio-depressants, fibroblast-depleting agents and/or anti-lipidic agents, may enhance drug penetration and improve therapeutic outcome. Besides, combination treatment can be employed to enhance anticancer immunity and defeat the immunosuppressive phenomena ubiquitous in malignancies (62). Researchers aim to exploit the immune system to eliminate cancer cells, including drug-resistant cells, through the use of immune checkpoint inhibitors combined with immunomodulatory agents or chemotherapy (63).

***Checkpoint Inhibitors: Unleashing the Immune System to Overcome Drug Resistance***

ICI is a new cancer therapy mode with the perspective of resisting drug treatment through the reinvigoration of the immune system of the body to attack and destroy cancerous cells (64). These inhibitors are specific to specific checkpoint proteins such as CTLA-4, PD-1 and PD-L1, normally regulating the activation of immune cells and preventing autoimmune responses. Cancerous cells readily utilize these checkpoints to avoid immune surveillance, so to speak, and essentially block an attack by immune cells (65). Checkpoint inhibitors help to inhibit these inhibitory signals and allow immune cells, in particular cytotoxic T lymphocytes (CTLs), to recognize and kill cancer cells. This modality of action is significantly different to conventional chemotherapeutics or precision medicines, which can target tumor cells directly and be susceptible to drug resistance mechanisms (66). Because checkpoint inhibitors stimulate the immune system of the patients, the anti-tumor effect can outlive therapy (67).

An example of the cancers where checkpoint inhibitors have been used effectively is melanoma, lung cancer, bladder cancer, and renal cell carcinoma. As an example, ipilimumab (CTLA-4 inhibitor) has shown significant effectiveness in the treatment of melanoma, extending the overall survival of some individuals (68). Similarly, PD-1 blockers such as nivolumab and pembrolizumab have revolutionised treatment in non-small cell lung cancer, particularly in high PD-L1 expressing or high mutational burden cancer. The same inhibitors have also presented possibilities in other cancers, like Hodgkin lymphoma and MSI-H colorectal cancer (45). The efficacy of checkpoint inhibitors is commonly correlated with the presence of tumor-infiltrating lymphocytes (TILs), and it is therefore suggested that these drugs require an existing immune response to be productive. However, in case of low TIL-expression in tumors, checkpoint blockade can very rarely lead to tumor regression (69).

In addition, when there is resistance to the other cancer medications, checkpoint inhibitors can be used to attack or prevent resistance to the cancer drugs. As a case in point, applying a BRAF inhibitor with a PD-1 inhibitor in melanoma was reported to reveal enhanced efficacy as compared with BRAF monotherapy, preventing the development of BRAF resistance (70). This demonstrates that checkpoint inhibition can reduce the development of resistant clones due to the selectivity of targeted therapy. Next, it has been shown that checkpoint inhibition can be utilized to make chemotherapy-resistant tumors sensitive to it in some cancers (71). The mechanisms through which checkpoint inhibitors circumvent drug resistance are complex and little known, but are most probably a combination of direct immune-mediated killing of resistant cells and modulation of the tumor microenvironment (72).

Despite the extraordinary efficacy of checkpoint inhibitors, these agents have limitations. A few people respond to these therapies, and some may experience immune-related side effects (73). The current research is focused on revealing biomarkers that predict sensitivity to checkpoint inhibition, determining a method of overcoming resistance to those drugs, and exploring new immunotherapies including conjunction immunotherapies and adoptive cell therapies (74). Checkpoint inhibitors have been combined with other immunomodulatory agents, including agonists of other types of stimulatory immunological receptors or antagonists of immunosuppressant molecules, with promise to further improve antitumor immunity and overcome resistance. Further inquiry and development of immunotherapeutic methods are essential to the improvement of options available to cancer patients and in addressing the issue of medication resistance (75).

***Nanomedicine: a novel approach to overcoming drug resistance***

Nanomedicine provides new solutions to address drug resistance in cancer by enhancing the delivery of drugs, increasing drug efficiency and changing the drug resistance property of the tumor microenvironment. The chemotherapeutic drug may be incorporated into nanocarriers, including liposomes, polymeric nanoparticles, and dendrimers, which shield drugs against premature degradation

in the body and non-specific distribution (75). This localized treatment can reduce the off-target toxicity and enable the drug at increased concentrations at the tumor site, including cancer cells resistant to drugs. Moreover, it is also possible to design nanocarriers to specifically target the tumour cells by conjugating ligands specific to the overexpressed receptors on the tumour cell surface (76). This active targeting increases the drug uptake of cancer cells that benefits the therapeutic index in addition to reducing exposure of non-cancerous cells to toxic substances of the drug. The nanomaterials can also be made responsive to a certain local stimulus in the tumor site, like pH, redox potential and enzyme activity. Such stimuli-sensitive nanocarriers may be used to deliver their payload specifically to the tumor location, increasing drug efficacy and reducing systemic toxicity (77).

Besides better drug delivery, nanomedicine has also been applied to overcome drug resistance-specific mechanisms. Another example is multidrug resistance (MDR), whereby there is usually an overexpression of efflux pumps, such as P-glycoprotein, active efflux pumps that pump drugs out of the cancer cells. Nanocarriers may shelter drugs against these efflux pumps, overcoming this resistance mechanism to reach their intracellular target (78). Moreover, nanocarriers may be preconfigured to introduce a combination of drugs at once, including drugs that act through distinct resistance pathways. This mixed treatment regimen may be very effective in hindering or surmounting drug resistance, where it may be harder to have the cancer cells resist multiple drugs simultaneously (79). Nanomaterials can also be employed to encapsulate gene therapy agents, including siRNAs or miRNAs, to silence genes imparting drug resistance and re-sensitize cancer cells to drugs (80). Nanoparticle-mediated delivery to target P-glycoprotein with siRNA has been demonstrated to overcome MDR in several types of cancer cell lines. This flexibility of nanomedicine holds the potential to formulate patient-specific anticancer therapies that can be customized to meet the unique drug resistance situations within a given tumor (81).

## DISCUSSION

Drug resistance is a peculiar obstacle in cancer treatment, and these implications are significant in relation to the efficacy levels of the actions and patient outcomes. As mentioned above, the pathways that generate drug resistance are versatile, possessing many dimensions, including genetic mutation, epigenetic alterations, altered drug metabolism, raised DNA repair, efflux pump activity and the tumor microenvironment (82). This has necessitated an all-embracing approach to the fight against drug resistance, including the development of new medications, the refinement of existing treatment protocols, and improvement in the complex interplay between cancer cells and the surrounding tissue (83). The recent advances in molecular biology, such as next-generation sequencing and CRISPR-Cas9 gene editing have provided us with much-needed resources to deconstruct the genetic basis of drug resistance, posing the opportunity to identify novel therapeutic targets and biomarkers. This evidence has stimulated the introduction of new classes of treatment strategies such as next-generation inhibitors, combination therapies, immunotherapies, and nanomedicine techniques, all aimed at fighting off or evading drug resistance (84).

To drive the development and resistance of cancer, there are certain molecular alterations unique to cancer, and combination therapy rationally designed to target these alterations has been promising. Such combinations can bypass or thwart resistance, as they target so many routes or processes simultaneously (85). Immunotherapy, and immune checkpoint inhibitors in particular, have become a revolution in the area of cancer treatment by engaging the ability of the immune system to attack and destroy cancer cells even when they have acquired resistance towards medication. Nanotechnology provides a new strategic framework for therapy, with enhanced transport of drugs, enhancing the efficacy of treatment and changing the tumor micro-environment (86). Nanocarriers can prevent the degradation, deliver them directly to cancer cells and even avoid efflux pump operation, which also raises new hopes to

overcome multidrug resistance. This multifaceted approach, comprising new strategies such as personalized medicine strategies through genetic profiling of the tumor cells in the individual, presents an immense opportunity to enhance the outcomes of cancer treatment (87).

However, there are certain boundaries, even with all the developments that have been made over the past few years. It is impossible to state which patients develop resistance to the medication and what resistance systems are involved. Although some biomarkers have been identified, more research is needed to implement better and comprehensive predictive systems (88). Moreover, the research of new medicines and treatments is quite difficult and costly. Clinical trials are necessary to verify the safety and effectiveness of new treatments; however, such a process is time-consuming and may not always work out. Lastly, cost and supply may act as a barrier to the accessibility of these advanced therapies, a disparity that may pose risks to cancer hemispheres (89).

Some exciting research directions have prospects. Non-invasive tumor profiling techniques can provide a viable alternative to patient biopsies because liquid biopsies provide a means to monitor a response to treatment as well as the acquisition of drug resistance (90). Machine learning and artificial intelligence technology are being used to analyze large amounts of data generated through the study of cancer genomes and proteins, and in vivo trials to identify new drug targets and to predict treatment responses (91).

## CONCLUSION

Improved nanocarriers, which could deliver several drugs or gene therapy agents together, are being developed and have a lot of potential in defeating multifactorial forms of drug resistance. Further investigation of the tumor microenvironment and its contribution to drug resistance will open the path to a novel approach to the development of therapies that act not only against the cancer cells but also influence the supporting cells and the microenvironment as well. By improving the present shortcomings and by working on the following directions, these strategies may ultimately enable the comprehensive overcoming of drug resistance in cancer therapy as a primary impediment to effective cancer treatment.

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**Conflict of Interest**

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**Consent for publication**

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